

Dear Readers,

I wish to thank all of you again for your emails and questions. Hearing from you is always a pleasure for me. I enjoy knowing that you read the newsletter in detail and I appreciate that you pass it on to your friends and colleagues. Please let me know if there are specific topics that you wish addressed.

Best regards,

Dr. Silvana Martino



# Breast Cancer Advisor

BY DR. SILVANA MARTINO • April 2013

## BIOLOGY BASICS

### Breast Cancer in Men

Up to now, the emphases of this newsletter has been on breast cancer in women. In this, and the next several issues, I want to address the topic of breast cancer in men.

There has always been a tendency to forget that breast cancer does occur in men. Consequently, the diagnosis of breast cancer in men is often made later because neither the men themselves nor their doctors tend to consider the possibility that a breast discomfort in a man may be cancer. The male breast is rarely examined as part of a routine physician visit. Unlike the recommendations for women, there is no screening test advised for breast cancer in men. Therefore, the diagnosis is always made as a result of symptoms.

Though the male breast is generally smaller than the female breast, its anatomy is similar. The one important difference is that the male

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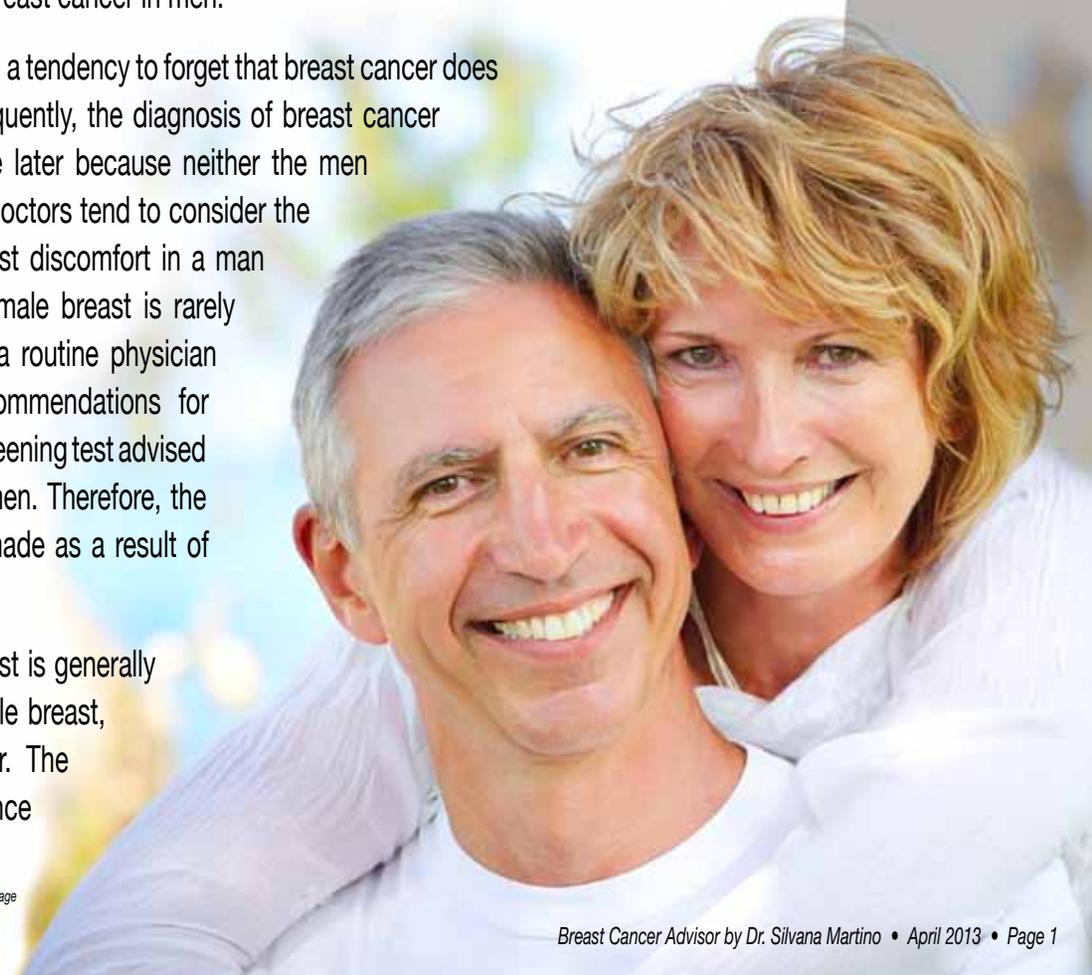
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## Biology Basics continued

breast is composed primarily of ductal structures and has minimal lobular structures compared to the female breast. (For a review of the anatomy of the breast, please refer to the August, 2011 issue of the Breast Cancer Advisor) For this reason, lobular carcinoma is rare in men. Ductal carcinoma is almost always what occurs. Paget's disease of the breast, a type of breast cancer that involves the nipple and areola, is somewhat more common in men than in women. Inflammatory breast cancer and bilateral breast cancer are rare in men.

In the U.S., 2,240 new cases of male breast cancer and 410 male breast cancer deaths are predicted to occur in 2013. For many decades, the ratio of one male for every 100 female cases of breast cancer has remained relatively constant. Though breast cancer in men can be seen at any age, the median age at diagnosis is about age 68. When compared stage for stage, the survival between men and women with breast cancer is the same. However, it is clear that men present at more advanced stages in part because the smaller size of the male breast leads to more direct extension by the tumor into the chest wall and the skin, but also because the under appreciation that breast cancer can occur in men leads to a longer delay in diagnosis.

Most of the breast tissue in men is located under the nipple and areola; consequently, this is the most common location of male breast cancer. The upper outer quadrant is the second most common location. A painless mass is the usual presentation, though other findings can occur and are similar to the symptoms found in women. These include : (1) a thickening in the breast, (2) a change in the size or shape of the breast, (3) a changes in the skin

of the breast such as redness, rash or dimpling, (4) changes of the nipple area such as a rash, itchiness or scaling, (5) a change in the direction or orientation of the nipple including inversion, (6) a mass under the armpit, (7) a discharge or bleeding from the nipple, and (8) a sensation of tightness or firmness of the chest wall under or near the breast. As with women, many findings turn out to be benign.

The evaluation of a breast complaint in a man should begin with a thorough history and physical exam by a medical professional. Not only does the breast need to be examined, but also the rest of the body looking for signs of tumor extension to lymph nodes and to other organs. Mammography can be done and is useful in assisting with a diagnosis. An ultrasound or breast MRI can also be added if needed to clarify the size and extent of disease. The next step is a biopsy. As in women, evaluation of the biopsy tissue should include hormonal receptors (estrogen and progesterone) and HER2 neu testing. Up to 90% of male breast cancers are hormone positive. Most are HER2 negative. However, they can be hormone negative, HER2 positive or triple negative.

In the next issue, I will discuss the treatment of male breast cancer once a diagnosis is made.

## BIOGRAPHY

### Dr. Silvana Martino

is the Director of Breast Cancer Research and Education at The Angeles Clinic Foundation in Santa Monica, California. She is board certified in internal medicine and medical oncology. Dr. Martino has specialized in the treatment and research of breast cancer for over three decades. She is a nationally recognized leader in the field of breast cancer. Her body of work has included research in breast cancer prevention, treatments for early breast cancer and metastatic disease. Dr. Martino has conducted and coordinated large national and international studies which have resulted in changing the standard of care worldwide.

DR. MARTINO'S  
CURRICULUM VITAE

# WHAT'S NEW

## Risk of Heart Disease After Radiation Therapy for Breast Cancer

Radiation therapy is commonly used in the treatment of breast cancer. The frequency of its use has increased for several reasons: (1) breast sparing surgery or lumpectomy has replaced mastectomy as standard surgical therapy, (2) ductal carcinoma in situ (DCIS) is more prevalent as we increase screening mammography in a population, and (3) data have shown that after a mastectomy, even in women with as few as 1-3 positive lymph nodes, radiation decreases recurrence and may increase survival. Though the value of radiation in the treatment of breast cancer is clear, there has always been a concern about the damage that this therapy causes to the areas surrounding the breast and the lymph nodes. Ideally, one wants to only radiate the breast and the lymph nodes. However, the ribs, lungs, heart, muscles, nerve tissue, lymph and blood vessels are close by and intermingled with the target tissues. They cannot be completely separated. Consequently, collateral damage invariably occurs. Considerable attention and skill are required in planning the radiation such that minimal damage is done to surrounding benign tissues.

In this context, the heart has been a major organ of concern. Many articles have been written about this problem and how to avoid it. A recent report was

published by Dr. Sarah Darby and colleagues from the Clinical Trial Service Unit and the George Centre for Healthcare Innovation, University of Oxford, Oxford and the Department of Medical Physics, Royal Surrey County Hospital and Surrey University, Guildford - both in the United Kingdom in the March 14, 2013 issue of The New England Journal of Medicine.

They conducted a population-based, case-control study of coronary events (heart events) in 2,168 women who underwent radiation therapy for breast cancer between 1958 and 2001 in Sweden and Denmark. The study included 963 women with a major coronary event and 1,205 controls. Using information for individual patients obtained from their hospital records, they calculated the mean radiation doses given to the whole heart and to one of the heart's main blood vessels. The types of heart event problems that they looked at were the more serious events; specifically, heart attacks, vascular surgery to the heart, and death from ischemic heart disease. They did not report on other types of heart problems such as rhythm problems, chest pain (angina), strokes, or congestive heart failure. Therefore, their analysis probably underestimates the magnitude of the problem.

This study provides several important conclusions: (1) the

exposure of the heart to radiation therapy increases the risk of heart disease, and there does not appear to be a minimum level below which there is not an increase in

cardiac events, (2) an increase in cardiac events is apparent within the first five years after radiation and continues for at least two decades, (3) women with radiation to the left breast had more cardiac events than women radiated on the right side since most of the heart is located on the left side of the chest area, (4) women with a preexisting history of heart disease had more cardiac problems from radiation than women without prior heart disease, and (5) rates of coronary problems were also increased in women who were diabetic, had chronic obstructive lung disease, were smokers, used pain medicine on a regular basis and those who were more obese.

This study included too few women who were age 40 or younger when they received radiation; so from this study, we do not know whether the effect of radiation to their heart would be more or less of a problem. In addition, very few of these women were treated with drug therapies that independently also cause heart damage such as Adriamycin, Herceptin or the taxanes. Since these are therapies in common use now, it is likely that the risk to the heart may be increased even more.

*The types of heart event problems that they looked at were the more serious events. Specifically, heart attacks, vascular surgery to the heart, and death from ischemic heart disease.*

## What's New continued

Perhaps the best way to conceptualize this issue is to realize that, because our treatment of breast cancer has resulted in considerable success, we now have a large number of “long-term survivors.” This has forced us to pay attention to the long-term side effects of our therapies. As these long-term side effects are recognized, we must seriously consider ways to reduce or prevent them. Collateral damage from our therapies must be recognized and dealt with. We cannot cure people of their breast cancer and then have them suffer from heart disease, leukemia, infertility, nerve damage and other toxicities.

Radiation oncologists have been aware of the problem of secondary heart damage from radiation therapy. Many techniques have been developed to try to minimize radiation to the heart. The most up-to-date technique that I am aware of is the Calypso System. It is not yet in common use for breast cancer therapy. Our own center has recently acquired this system. It has the ability to give radiation in a manner synchronized to a patient's breathing, taking advantage of the fact that when you take a deep breath the chest and breast area are lifted away from the internal organs thus greatly reducing radiation exposure to the heart. I will provide further detail on this system in an upcoming issue.

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## Pre-Operative MRI in the Newly Diagnosed Breast Cancer Patient — Does it Affect Outcome?

Mammograms have been the main imaging modality for breast cancer diagnosis since the initial breast cancer screening trials in the 1970's. However, mammography has its limitations, including under-estimation of tumor size and inability to detect cancer in dense breast tissue. The last decade has seen the increased use of bilateral breast magnetic resonance imaging (MRI) because it is more sensitive at detecting breast cancer than digital mammography, particularly in women with dense breasts. Additionally, breast MRI has been shown to be more accurate at estimating tumor size. Indeed, bilateral breast MRI is recommended for breast cancer screening in women with a genetic predisposition to breast cancer.



However, there remains much debate regarding the role of MRI in the patient with a new diagnosis of breast cancer. Currently, up to 40% of breast cancer patients who elect breast conservation require additional surgery or re-excision because of tumor

cells at the edge of the excised tissue. A multi-center study from the American College of Radiology Imaging Network (ACRIN 6667) reported that MRI detected additional disease in up to 30% of breast cancer patients with 3% found to have cancer in the opposite breast. Since breast MRI is more sensitive than mammography and can better estimate tumor size, can routine pre-operative breast MRI translate into fewer patients requiring additional surgery for positive tumor margins? And do breast cancer patients who have a pre-operative MRI have a lower rate of breast recurrence?

Intuitively, one would expect that since MRI is better at detecting breast cancer, it would provide a better map for surgeons resulting in less additional surgeries or re-excisions. There have been two randomized prospective trials evaluating the impact of MRI on positive tumor margin rate—COMICE (Comparative Effectiveness of MRI in Breast Cancer) trial from the United Kingdom<sup>1</sup> and the MONET (MR Mammography of Non-Palpable Breast Tumors) trial from the Netherlands.<sup>2</sup> In both trials,

*continued next page*

Guest Writer continued

there was no difference in the rate of positive tumor margins between the group that had a pre-operative MRI and the group that did not. This translated into equivalent re-excision rates in the two arms of the trial (Table 1). Surprisingly, the patients in the MONET study who had a pre-operative MRI had a higher re-excision rate than the control group. A recent meta-analysis of published series showed a similar re-excision rate of 11% regardless of whether a patient had a pre-operative breast MRI<sup>3</sup>, suggesting that pre-operative MRI does not result in a decreased need for re-excision in cancer patients electing breast conservation.

*Surprisingly, the patients in the MONET study who had a pre-operative MRI had a higher re-excision rate than the control group.*

results from the COMICE trial suggest that pre-operative breast MRI does not influence breast recurrence rate, but these unpublished results have a limited follow-up period. Since local recurrence does not alter overall survival, it is not surprising that pre-operative breast MRI has had no impact on survival.

In conclusion, the routine use of pre-operative use of breast MRI does not decrease the need for re-excision in breast cancer patients electing breast conservation surgery and does not result in a decrease in local

Another way of evaluating the impact of pre-operative breast MRI is to evaluate the number of recurrences in the breast or the local recurrence rate (Table 2). Fisher et al, reported a local recurrence rate of 1.2% and 6.8% at 40 months in patients that did, or did not, have a pre-operative MRI.<sup>4</sup> Other published series have not shown a difference in breast recurrence based on pre-operative MRI use.<sup>5,6</sup> Preliminary

SERIES		No.	PERIOD	LOCAL RECURRENCE RATE	
FISCHER ET AL <sup>4</sup>	MRI	86	1993-1997	1.2%	P<0.001
	No MRI	138		6.8%	
SOLIN ET AL <sup>5</sup>	MRI	215	1992-2001	8 YEAR: 3%	P=.51
	No MRI	541		8 YEAR: 4%	
HWANG ET AL <sup>6</sup>	MRI	127	1999-2005	8 YEAR: 1.8%	P=0.67

Table 2. Impact of pre-operative MRI on local recurrence rate

recurrence. Although pre-operative breast MRI does detect contra-lateral breast cancers, the incidence is low. The use of breast MRI in the newly diagnosed breast cancer patient should be individualized and not used routinely.

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SERIES		No.	RE-EXCISION RATE	ADDITIONAL SURGERY	MASTECTOMY
COMICE <sup>1</sup>	MRI	816	10%	16%	13%
	No MRI	807	11%	19%	9%
MONET <sup>2</sup>	MRI	74	34%	45%	39%
	No MRI	75	12%	28%	45%
META-ANALYSIS <sup>3</sup>	MRI	-	11.6%	18%	26%
	No MRI	-	11.4%	19%	18%

Table 1. Impact of MRI on re-excision rate in breast cancer patients electing breast conservation

# QUESTIONS & ANSWERS

(Q) Dr. Martino, A friend of mine told me that lymph nodes are no longer removed when there is a diagnosis of breast cancer. Is this true?

(A) It is still standard of care to investigate the status of lymph nodes when there is a diagnosis of invasive breast cancer. In the past, this was done with a “lymph node dissection,” at which time the surgeon most often resected level one and level two axillary lymph node areas under the arm. Today, most modern surgeons perform a “sentinel lymph node” procedure which removes considerably fewer lymph nodes. A subsequent decision as to whether more nodes need to be removed is then based on the results from the sentinel node procedure. In patients who have non-invasive breast cancer (DCIS), the decision to evaluate lymph nodes is more variable. If the lesion is large or of high grade, the surgeon may perform a sentinel node procedure. If the lesion is small and of a lower grade, the surgeon will often avoid lymph node evaluation. If at any time the nodes are palpable and feel abnormal, they are evaluated with a biopsy or resection.

(Q) Dr. Martino, I am receiving chemotherapy for breast cancer and I am tolerating it pretty well. I know from talking to other patients that they are also receiving Neulasta to help them with their blood counts. My doctor says that I don't need it. I don't understand why. Won't it help me with my blood counts too?

(A) Drugs like Neulasta and Neupogen are often used to reduce the lowering of white blood cells counts that occur with most chemotherapy drugs. The reason why this is important is because you are more likely to develop an infection when your white blood cell count is down. Not all chemotherapy drugs lower blood counts to the same degree, however. The decision to add Neupogen or Neulasta to your own chemotherapy program is a decision that your oncologist makes based on what chemotherapy drugs you are being given and how likely it is that your counts will go down, how long they are likely to stay down before they recover and your own overall medical condition.

E-mail your questions to:  
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